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13. ABSTRACT ***(Maximum 200 Words)***

Since the overall risks and benefits of hormonal replacement therapy (HRT) in breast cancer survivors are not clearly established, and it is unlikely that a definitive answer will be available in the near future, we developed a decision analytic computer model for individualizing decisions, using the best available literature estimates for all currently known or suspected benefits and adverse outcomes. In addition, the model allows input of individual risk factors for breast cancer recurrence, coronary artery disease, osteoporosis, etc., and allows weighting of patients' preferences for these outcomes. We found that women at average risk for coronary heart disease (CHD) and hip fracture lose 4.3 quality-adjusted life months (QALMs) by taking HRT. Women who value the CHD and hip fracture states as having the worst impact on health and breast cancer recurrence as having the mildest impact on health lose the least from HRT, 3.6 QALMs. Women who value the CHD and hip fracture states as having the mildest impact and breast cancer recurrence as having the worst impact on health lose 5.3 QALMS. Therefore, unless future studies show a larger benefit on CHD mortality or other health states, HRT decisions for breast cancer survivors should include careful consideration of individual preferences for all of the potential outcomes. The model can readily incorporate data on new treatments and other outcomes as they become available.

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INTRODUCTION

The benefits and risks of hormone replacement therapy (HRT) for post-menopausal women have been studied extensively, and yet for most women the choice remains one of uncertainty. HRT is widely believed to decrease the future risk of breast and endometrial cancer. The addition of progestin to estrogen is believed to eliminate the increased risk of endometrial cancer, but may also lessen the preventive effect on coronary heart disease risk. HRT is also known to affect serum lipoproteins, sexual function, and urinary function, and it can cause endometrial hyperplasia and other adverse effects, and may require invasive monitoring procedures. Although the American College of Physicians and others have studied HRT and provide guidelines for women with a variety of risk factors, none of the recommendations apply to women with a history of breast cancer. In addition, the guidelines apply to population groups and not to individuals. Any individual may value a health state, an intervention, or the future risk of an illness differently than do others. Personal decisions regarding preventive medicine therefore should reflect these valuations.

It is widely believed that HRT is contraindicated in postmenopausal women who have had breast cancer. However, HRT has not been adequately studied among breast cancer survivors. The detection of early breast cancer has increased dramatically during the last decade accompanied with a rise in five year survival of treated patients, so there are many women who need guidance. There are approximately 182,000 new cases of breast cancer in women in the U.S. per year. Since the majority of these women will have localized disease can expect to survive 20 years or more, they will face risks of vascular and bone disease similar to those without a history of breast cancer. The induction of premature menopause with adjuvant chemotherapy increases the risk of coronary artery disease and osteoporosis among these women. The prohibition of HRT may diminish overall survival and quality of life among breast cancer survivors despite higher risk of endometrial and breast carcinoma with this intervention.

Until the results of clinical trials of HRT in breast cancer survivors are available, which will take many years, it will remain uncertain as to wether this population of women should be given HRT. While we await such results, we are developing a decision analysis method utilizing a mathematical model to provide guidance for women with breast cancer as to wether they should take HRT.

We are requesting an unfunded continuation for one year to complete analysis and write paper.

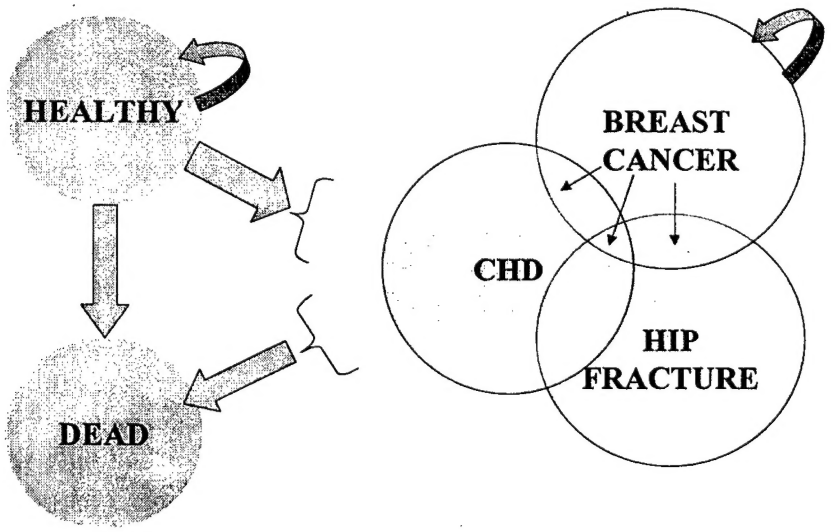
BODY

METHODS

A decision analysis was performed for 60-year old women breast cancer survivors who are considering hormone replacement therapy (HRT) as preventive medicine for coronary heart disease (CHD) and osteoporosis. The outcome measure was quality-adjusted life months (QALMs) life expectancy with each option. A base case analysis was performed for women at average risk for CHD and osteoporosis. A sensitivity analysis was performed for women at higher or lower risks for each disease. HRT was assumed to be combined estrogen and progesterone for women with intact uteruses or estrogen alone for women who have had hysterectomies.

The decision analysis was performed with a Markov transition state model (DATA, TreeAge Software, Williamstown, MA). The model begins with two hypothetical cohorts of healthy women, one choosing HRT and one declining it. Each year some women develop CHD, hip fracture, breast cancer, or combinations of these diseases. Each year they also risk death from these diseases or from other general population causes related to their age, sex and race (Vital Statistics).

Markov Model



For simplicity, the transitions between the CHD and HIP fracture state and other states are not shown; they are the same as for the breast cancer state.

RESULTS

The assumptions used in the analysis for these risks and the effect of HRT on the risks are shown in table 1. Rates taken from the literature were transformed to probabilities for use in the model.

TABLE 1: ASSUMPTION

OUTCOME	RATE OR PROBABILITY	RELATIVE RISK	REFERENCE
Breast Cancer Recurrence	Cumulative Recurrence Yr 1, 11% Yr 5, 41.2% Yr 10, 56%	———	Early Breast Cancer Trialists Collaborative Group
CHD Risk	Annual Probability 0.21% at age 50 yrs to 0.48% at age 60 yrs and greater	———	Lloyd-Jones
Hip Fracture Incidence	Incidence, per 100,000 White women, 33.9 at age 50.1 yrs to 1731.5 at age 80 yrs Nonwhite women, 18.4 at age 50 yrs to 880.6 at age 80 yrs	———	Farmer ME
Effect of HRT on Breast Cancer Risk	———	Any Use 1.27	Collab. Grp. On Hormonal Factors in Br. Cancer
Effect of HRT on Hip Fracture Risk	———	0.75	Grady D, et al
Effect of HRT on CAD Risk	———	Yr 1 1.52 (1.01-2.29) 2 0.98 (0.66-1.46) 3 0.85 (0.54-1.33) ≥4 0.75(0.50-1.13)	Herrington
Annual Risk of Dying after developing Breast Cancer	Disease specific mortality probability 0.0324		Early Breast Cancer Trialists Group
Ann Risk of Dying after developing CHD	9.6% in first yr 2.6% in subsequent yrs		Col
Ann Risk of Dying after Hip Fracture	17% in first yr		Col

Utilities (Table 2)

We conducted interviews on a convenience sample of 30 women from the breast cancer clinics at 2 tertiary care centers to assess their utilities. Using a computerized interview equipped with the U-titer II program (Sumner), women assigned a utility to each potential health state by means of the standard gamble technique. [We also measure utilities for some of the states using a visual analog scale]. Health state descriptions were developed for both acute and chronic scenarios for outcomes relevant to use of HRT. The acute states lasted 6 months and resolved completely with return to current health. For these states the women gambled the health state versus some probability of ideal health or 6 months of severe, constant pain, with the choices following a bisection of probabilities. The chronic health states were described as stable conditions that last for the remainder of the woman's life expectancy, which was calculated from a simple life table. These states were developed using an adaptation of Torrance's Health Utility Index II and included 8 key dimensions. For these states the women gambled the health state versus some probability of ideal health or death, again with the choices following a bisection of probabilities. The utilities for each state are shown in Table 2.

Table 2 Utilities of chronic health states

Health States Median (Interquartile Range)	Overall N=81	Breast Clinic N=30	GIM Clinic N=51
Current Health	.99 (.93-1)	.98 (.93-1)	1 (.92-1)
KEY CHRONIC STATES			
Stage I breast cancer	.98 (.91-1)	.99 (.93-1)	.97 (.90-1)
Cyclic HRT	1 (.95-1)	.99 (.95-1)	1 (.93-1)
Chronic angina (class III)	.90 (.59-.98)	.91 (.75-.97)	.90 (.5-.99)
Post hip fracture, poor result	.84 (.50-.93) *	.89 (.75-.93)	.75 (.02-.93)
Constant Pain (6 mo.)	.93 (.61-1)	.96 (.75-.99)	.93 (.59-1)
OTHER CHRONIC STATES			
Metastatic Breast Cancer	0 (0-.50) N=19	0 (0-.50) N=11	.06 (0-.37) N=8
Post Vertebral Fracture	.97 (.86-.98) N=21	.98 (.93-.98) N=10	.86 (.74-.99) N=11
Chronic menopausal problems	.99 (.93-1) N=16	1 (.99-1) N=6	.96 (.93-1) N=10
Alzheimer's Disease	.24 (0-.5) N=18	.49 (0-.75) N=3	0 (0-.5) N=15
Chronic Post CVA	.61 (.26-.75) N=13	.5 (.41-.74) N=3	.68 (.24-.96) N=10

* $p<.05$ for Wilcoxon Rank Sum comparison between 2 groups.

Table 3. Utilities of acute health states

Health States Median (Interquartile Range)	Overall *	Breast Clinic	GIM Clinic
KEY ACUTE STATES			
Acute MI	.97 (.89-1) N=25	.97 (.89-1) N=11	.97 (.83-1) N=14
Acute Hip Fracture	.99 (.90-1) N=23	1 (.93-1) N=6	.98 (.90-1) N=17
New Breast Cancer	1 (.85-1) N=19	.99 (.87-1) N=7	1 (.77-1) N=12
Acute Menopausal Symptoms	1 (1-1) N=14	1 (1-1) N=6	1 (.96-1) N=8
Health States Median (Interquartile Range)	**Overall** *	**Breast Clinic**	**GIM Clinic**
OTHER ACUTE STATES			
Vaginal Bleeding	1 (1-1) N=10	1 (1-1) N=2	1 (1-1) N=8
Acute DVT	1 (.71-1) N=10	1 (1-1) N=4	.74 (.33-1) N=6
Acute PE	.99 (.79-1) N=11	.99 (.97-.99) N=5	.90 (.49-1) N=6
New Colon Cancer	1 (.99-1) N=8	1 (1-1) N=3	1 (.98-1) N=5
Acute CVA	.98 (.95-1) N=13	.99 (.95-1) N=7	.97 (.59-1) N=6
Acute Cholecystitis	1 (1-1) N=11	1 (.98-1) N=4	1 (1-1) N=7

* Utilities were not significantly different between the 2 groups.

Table 4

Demographic Characteristic	Overall N=81	Breast Clinic N=30	GIM Clinic N=51	p *
Mean Age (SD)	61	61	61	.98
Race (%)				.02
African American	29	10	41	
White	83	54	65	
Other	7	4	5	
Education (%)				.003
High school	36	13	50	
Some college or college	35	43	30	
Some graduate school	29	43	20	
Household Income (%)				.004
< $20,000	14	7	19	
$ 20- 59,999	43	26	53	
> 60,000	43	67	28	
Married (%)	56	77	44	.004

* p-value for Chi^2 except as noted

† p-value for t-test

Characteristic	Overall N=81	Breast Clinic N=30	GIM Clinic N=51	p
Past Medical History (%)				
Breast Cancer	39	100	0	<.001
Coronary Heart Disease	16	16	16	.96
Osteoporosis	11	16	8	.24
Medications (%)				
HRT Current	29	0	47	
HRT Past	32	55	18	<.001
Tamoxifen Ever	19	51	0	<.001
Oral contraceptives ever	40	45	37	.48
Family History (%)				
Breast Cancer	28	26	29	.72
Coronary Heart Disease	60	58	61	.81
Osteoporosis	18	32	12	.02

DISCUSSION

- Estimated benefits from HRT vary with
  - Risk status
  - Race
  - Age
  - Utilities assigned to health states

- The largest difference comes from choice of source of estimate for benefit on CAD- currently there are no clear answers. Women and their physicians must choose between

  1) a large amount of observational data which suggests a large benefit
  2) a small amount of RCT data (on a different question - 2° prevention) which shows a small benefit

- For BCS, the only conditions that result in gains in quality-adjusted life expectancy are combinations of the most optimistic assumptions regarding quality of life with breast cancer and the effect of HRT on the risk of breast cancer recurrence and the most pessimistic assumptions regarding quality of life with CHD and hip fracture and the effect of HRT on the risk of CHD and hip fracture.

Limitations

- Not all outcomes potentially affected by HRT are included in the model. (e.g.: Alzheimer's disease, colon cancer, stroke)

- Not all possible interventions are included in the model. (e.g.: raloxifene, alendronate, statins)

KEY RESEARCH ACCOMPLISHMENTS

- Women at average risk for CHD and hip fracture lose 4.3 QALMS by taking HRT.
- Women who value the CHD and hip fracture states as having the worst impact on health and the breast cancer state as having the mildest impact on health lose the least from HRT, 3.6 QALMS.
- Women who value the CHD and hip fracture states as having the mildest impact on health and the breast cancer state as having the worst impact on health lose 5.3 QALMS.
- Depending on the utility values chosen for health states and on individuals' risk factors for disease, HRT results in a loss of 0.2 QALMS (for women with a high risk for CHD and hip fracture) or a loss of 6.1 QALMs (for women with a low risk for CHD and hip fracture).
- Our base case analysis used the HRT effect on CHD risk found in the HERS trial, an increased risk in the first year, then a decrease in risk by year 3. In a sensitivity analysis, we calculated outcomes using the HRT effect on CHD risk found in observational studies, a relative risk of 0.51. The benefits of HRT are somewhat greater under these conditions. Depending on the utility values chosen for health states and on individuals' risk factors for disease, HRT results in gains in quality-adjusted life expectancy as great as 3.3 QALMs or losses as great as 5.4 QALMs.

REPORTABLE OUTCOMES

Our results were presented at the Society for General Internal Medicine national meeting in Boston, MA, May, 2000, and at the DOD Era of Hope meeting Atlanta, GA, June, 2000.

CONCLUSIONS

Unless future studies show a larger benefit on CHD mortality or other health states, HRT decisions for BCS should include careful consideration of individual preferences for all of the potential outcomes. The model can readily incorporate data on new treatments and other outcomes as they become available.

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Email: grants@mssm.edu

Date: June 6, 2000

GCO Project # 95-545 0001 03 CM (X)
Principal Investigator
Henry Sacks, M.D., PH.D.

Department of the Army

Dear Sir/Madam,

The project entitled **HORMONAL REPLACEMENT THERAPY FOR BREAST CANCER SURVIVORS: A DECISION ANALYSIS** includes activities involving human subjects. The Institutional Review Board of the Mount Sinai School of Medicine reviewed this project by expedited review in accordance with our assurance to the Department of Health and Human Services **M-1155**. The project is approved for continuation for the period **7/1/00** through **6/30/01.**

Sincerely yours,

Joseph S. Eisenman, Ph.D.
Vice-Chairperson
Institutional Review Board

Institutional Review Board Posting

From: Elan Czeisler, Compliance Officer
Institutional Review Board
East Building 4-79 Box 1075
Extension 88980

IRB Approval Date: 7 June, 2000

95-545 (0001) 03 CM (X)
HORMONAL REPLACEMENT THERAPY FOR BREAST CANCER SURVIVORS: A DECISION ANALYSIS
Henry Sacks, M.D., PH.D.
This project was reviewed by expedited review is approved for continuation for the period **7/1/00** through **6/30/01**

No changes may be made to the protocol or to the consent form without IRB approval. Submit any proposed changes promptly in order to avoid delays. Please indicate the GCO project number on all pages. *When presenting revisions, please submit a memo explaining the changes as well as two copies of the consent form: one copy with all revisions highlighted and a clean copy to be stamped when granted final approval.*

Please Note: Any notices or advertisements recruiting subjects for this study or asking other physicians' cooperation in identifying potential subjects must be approved by the Institutional Review Board prior to distribution. All advertisements must include the GCO number and expiration date. If you have any questions, please call the IRB administrator at the number listed above.

DATE: June 30, 2000

PART I - RESEARCH PARTICIPANT INFORMATION SHEET:

TITLE: HORMONE REPLACEMENT THERAPY FOR BREAST CANCER SURVIVORS

PURPOSE OF THE STUDY

You are being asked to participate in a research study. You qualify for the study because you are a woman over 45.

The purpose of this study is to see how women feel about health problems relevant to the decision of whether or not to take hormone replacement therapy (estrogen) after menopause.

DESCRIPTION OF RESEARCH

If you agree to join this study we will ask you to take part in an interview that will last about 30 minutes. The interview will be conducted by a trained researcher using a computer. He or she will ask you about yourself, your health and any medical conditions you may have. Then the interviewer will describe different health scenarios, describing what life might be like with different health problems. You will be asked to indicate how you would feel if you had the health problems described in the scenarios. You will be asked to rate the scenarios in two different ways. First you will be asked to put them on a scale, in order from best to worst. Then you will be asked how much you would be willing to risk if you had the scenarios we describe in order to be completely healthy. These rating methods will be explained more fully to you with several examples. We will also need to review your medical record in order to obtain additional information about your health.

We will be interviewing 75 of women from the general medical clinic and 75 from the breast clinic. The information will be recorded using an identification number (an ID number).

COSTS REIMBURSEMENTS

We will give you $20 after completing the interview, for your time and expenses.

POTENTIAL RISKS AND DISCOMFORTS

Since this study involves only an interview, there should be no physical, social, financial or legal risk to you. It is possible that reading some of the health scenarios may be upsetting. If that happens, you may choose to skip over that health scenario, or stop completely. Every effort will be made to keep the information you give us confidential. When the results of the study are reported, your information will be combined with information from other women who join the study, and you will not be identified in any way.

POTENTIAL BENEFITS

We do not expect that you will benefit directly from this study. This information we gather may help improve the care of women in the future, particularly around the decision to use hormones after menopause.

ALTERNATIVES TO PARTICIPATION

You may choose not to participate. This will not affect your care in this clinic or elsewhere in any way.

CONFIDENTIALITY

Your identity as a participant in this research study will remain confidential. with respect to any publications of the results of this study. Your medical record in connection with this study will be kept confidential to the extent permitted by law. Furthermore, your medical record may be reviewed by government agencies or the agency sponsoring this research in accordance with applicable laws and regulations.

COMPENSATION TREATMENT

In the event of injury resulting from participation in the research study please contact Dr. Henry Sacks at 212-241-8254 and Mt Sinai will make available to you at your expense its hospital facilities and professional attention. Financial compensation from Mt Sinai is not available.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. You will suffer no penalty nor loss of any benefits to which you are otherwise entitled should you decide not to participate. Withdrawal from this research study will not affect your ability to receive alternative methods of medical care available at Mt Sinai Medical Center.

Significant new findings developed during the course of the research study which might be reasonably expected to affect your willingness to continue to participate in the research study will be provided to you.

TERMINATION OF PARTICIPATION

You may discontinue participation in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

PROBLEMS OR QUESTIONS

If you ever have questions about this study or in case of research-related injuries, you should contact Dr. Henry S. Sacks at telephone number 212-241-7856 of a representative from the Institutional Review Board at 212-659-8970.

MOUNT SINAI SCHOOL OF MEDICINE
CONSENT FOR RESEARCH

Authorization to Participate in Research

This form must be signed by the participant/surrogate and the investigator/delegate

Participant _____ _____
(Print Name) (Unit #)

1. I hereby volunteer to participate in a research program under the supervision of Dr. Henry S. Sacks and his/her associates at Mount Sinai School of Medicine.

2. I acknowledge that I have read, or had explained to me in a language I understand, the attached consent document and that _____ has explained to me the nature and purpose of these studies. This explanation included a description of the parts of the study that are experimental, the possible discomforts, symptoms, side effects and risks that I might reasonably expect, and the possible complications, if any, that I might reasonably experience from both known and unknown causes as a result of my participation in these studies. I have had the opportunity to ask questions I had about the study and all the questions I asked were answered to my satisfaction.

2. I understand that I am free to withdraw this authorization and to discontinue my participation in these studies at any time. The consequences and risks, if any, of withdrawing from the study while it is ongoing have been explained to me. I understand that such withdrawal will not affect my ability to receive medical care to which I might otherwise be entitled.

4. I confirm that I have read, or had read to me, this entire authorization and that all blanks or statements that require completion were, in fact properly completed before I signed this authorization.

Research Subject/ Surrogate: _____ Date: _____
(signature)

Name: _____ Time: _____
(print)

Relationship: _____
(if signed by surrogate)

For IRB Official Use Only
This Consent Document is approved for use by Mount Sinai's Institutional Review Board (IRB)

From: 7/27/00 To: 6/30/01

MOUNT SINAI SCHOOL OF MEDICINE
CONSENT FOR RESEARCH

Authorization to Participate in Research (continued)

(Title) **PRINCIPAL INVESTIGATOR**

For subjects who are not able to read this consent document themselves, the following must be completed:

I confirm that I have accurately translated and/or read the information to the subject:

Witness: _____
(signature)

Name: _____
(print)

Address: _____
Number and Street City State Zip Code

ATTESTATION OF PRINCIPAL INVESTIGATOR/DELEGATE:

I have fully explained to the above volunteer/relative/surrogate the nature and purpose of the above mentioned research program (including the extent to which the studies are experimental), the possible complications which may arise from both known and unknown causes as a result thereof and the consequences and risks, if any, if the subject decides to discontinue participation. I believe that he/she understands the nature purpose, and risk of these studies. I have also offered to answer any questions relating to these studies and have full and completely answered all such questions.

_____
(Signature of Principal Investigators/Delegate) (Date)

_____
(Print Name) (Title)

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From: 7/27/00 To: 6/30/01